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CLINICAL RESEARCH

Combination of copeptin and high-sensitivity cardiac troponin T assay in unstable angina and non-ST-segment elevation myocardial infarction: A pilot study

Mesure combinée de la troponine hyper-sensible et de la copeptine dans le diagnostic de l'angor instable de l'infarctus du myocarde sans sus-décalage du segment ST : une étude pilote

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Received 21 September 2010; received in revised form 1st November 2010; accepted 3 November 2010

Available online 22 December 2010

KEYWORDS

Cardiac troponin;
High-sensitivity
assay;
Copeptin;
Acute coronary
syndrome;
Unstable angina

Summary

Background. — High-sensitivity cardiac troponin assays have improved the detection of acute coronary syndrome.

Aim. — To examine the possible incremental value of copeptin in the detection of acute coronary syndrome.

Methods. — We designed a prospective cohort study to compare the performance of high-sensitivity cardiac troponin T (hs-cTnT) measured at admission in combination with copeptin, and the performance of hs-cTnT alone, measured at admission, 3 hours and 6 hours, in patients

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; cTn, cardiac troponin; cTnI, cardiac troponin I; cTnT, cardiac troponin T; CV, coefficient of variation; ECG, electrocardiogram; hs-cTn, high-sensitivity cardiac troponin; hs-cTnT, high-sensitivity cardiac troponin T; ROC, receiver operating characteristic.

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MOTS CLÉS

Troponine ;
Hyper-sensible ;
Copeptine ;
Syndrome coronarien
aigu ;
Angor instable

with suspected acute coronary syndrome of < 6 hours' duration after onset of symptoms (exclusion of patients with ST-segment elevation myocardial infarction).

Results. — Fifty-eight consecutive patients fulfilled our criteria and were included. After detailed investigations, the final adjudicated diagnosis was acute coronary syndrome in 30 patients (including acute myocardial infarction in 13 and unstable angina in 17) and non-acute coronary syndrome in 28 patients. Measured on admission, hs-cTnT concentration was > 14 ng/mL (99th percentile) in 22 patients with acute coronary syndrome; repetition of the measurement at 3 hours and 6 hours identified three and four additional patients, respectively. The combination of copeptin with hs-cTnT determined on admission identified 26 patients with acute coronary syndrome, with a negative predicted value of 82.6%. The area under the receiver operating characteristic curve was 0.90 for hs-cTnT measured on admission, and 0.94 if repeated at 3 hours and 6 hours or combined with copeptin measurement at admission (non-significant difference).

Conclusions. — This prospective study demonstrated that a dual marker strategy that combines hs-cTnT with copeptin increased slightly the detection of acute coronary syndrome at admission. © 2010 Elsevier Masson SAS. All rights reserved.

Résumé

Rationnel. — Les troponines hyper-sensibles (Tn-hs) améliorent la détection des syndromes coronariens aigus (SCA).

Objectif. — Étudier la possible amélioration de la détection des SCA offerte par l'association de copeptine avec la TnT-hs.

Méthodes. — Cohorte prospective qui a comparé les performances de TnT-hs mesurée à l'admission et associée à la copeptine, à la mesure de TnT-hs seule, à l'admission, trois heures et six heures, chez les patients suspects de SCA évoluant depuis moins de six heures (exclusion des patients avec infarctus du myocarde avec sus-décalage du segment ST).

Résultats. — Cinquante-huit patients consécutifs ont été inclus. Le diagnostic final était SCA chez 30 patients (13 patients avec IDM et 17 avec angor instable), et non-SCA pour 28 patients. Mesurée à l'admission, la TnT-hs était supérieure à 14 ng/mL (99^e percentile) chez 22 patients avec SCA. La répétition des dosages à trois heures a permis de détecter trois patients supplémentaires, et à six heures quatre patients supplémentaires. La mesure conjointe de copeptine et de TnT-hs a détecté 26 patients avec SCA, et sa valeur prédictive négative pour le diagnostic de SCA est de 82,6 %. L'aire sous la courbe de la courbe ROC est de 0,9 pour la TnT-hs mesurée à l'admission, 0,94 pour la mesure répétée à trois heures, six heures ou la mesure combinée de copeptine et de TnT-hs à l'admission (*p* non significatif).

Conclusion. — Cette cohorte prospective montre que l'utilisation combinée de copeptine et de TnT-hs à l'admission améliore modestement la détection des SCA.

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Background

The management of patients with chest pain-related symptoms remains an important clinical challenge [1]. The adequate ruling out of ACS in patients with chest pain is crucial, as the erroneous discharge of a patient with ACS is associated with a high risk of cardiac events [2,3]. Over the past decades, cTns have emerged as key biomarkers for patients with acute chest pain, and have undoubtedly improved the rate of detection of occult ACS [4–7]. hs-cTn assays have been developed recently, enabling measurements of concentrations that are ~10-fold lower than those previously measurable. Recent studies have confirmed the increased accuracy of these high-sensitivity assays compared with conventional assays in the early detection of AMI [8–10]. However, concerns have been raised about a possible specificity deficit with these new assays [11–13].

In addition, a second measurement of hs-cTn may be warranted in order to increase the accuracy of the assay [8,14]. Identification of the perfect biomarker remains an unmet need, and many researchers have advocated multimarker testing [15].

The arginine-vasopressin system plays a crucial role in the regulation of the individual endogenous stress response [16]. Previous studies have demonstrated that copeptin (the c-terminal part of the vasopressin prohormone) is increased in AMI [17–19]. Moreover, copeptin measurement adds valuable information to conventional assays of cTn in the early detection of AMI, according to two recent studies [17,19]. The possible merit of copeptin in addition to hs-cTn is unknown. This study examined the diagnostic accuracy of serial measurements of hs-cTn (at 0, 3 and 6 hours after admission) and of the combination of copeptin with hs-cTn measured on admission, in the detection of ACS.

Study population and methods

Between June and November 2009, we enrolled consecutive patients who were admitted to the Department of Cardiology of Cochin Hospital (Paris, France) for suspected recent ACS, defined as chest pain of ≤ 6 hours' duration since onset, suggestive of myocardial ischaemia, and lasting > 5 minutes at rest or upon minimal exertion. Patients presenting after a cardiac arrest or with ST-segment elevation myocardial infarction were excluded from the study.

This study was approved by the ethics committee of Cochin Hospital and all patients granted their written informed consent to participate.

Clinical assessment and investigations

Upon admission to the hospital, all patients underwent a detailed clinical evaluation, including medical history, 18-lead ECG, continuous bedside ECG monitoring, screening blood tests and chest X-ray. Decisions to obtain an echocardiogram or coronary angiograms were left to the discretion of the primary physicians. Analysis of cTn was done using a conventional cTnI assay for routine assessment of patients and an hs-cTnT assay for research purposes.

Conventional cardiac troponin I assay

Measurement of cTnI was done using an Xpand[®] HM analyser (Siemens Healthcare Diagnostics Inc., Newark, NJ, USA). The 99th percentile is achieved at $0.07 \mu\text{g/L}$ with a CV between 15 and 22%; a CV $\leq 10\%$ between measurements is achieved at $0.14 \mu\text{g/L}$.

High-sensitivity cardiac troponin T assay

Hs-cTnT (Roche Diagnostic, Meylan, France) was measured in heparinized samples collected on admission, and at 3 and 6 hours. The assay was performed on an Elecsys[®] 2010 analyser using an electrochemiluminescence immunoassay. The analytical performances of this assay have been previously reported; the 99th percentile with a CV $< 10\%$ is achieved at 14 ng/L [11]. In our laboratory, the CV was found to be $< 4\%$ (3.6% at 27.5 ng/L and 2.8% at 2.36 ng/L).

Copeptin measurements

Copeptin was measured in heparinized samples collected on admission. The assay was performed on a Kryptor[®] analyser using the commercial sandwich immunoluminometric assay (Brahms Copeptin Kryptor, Brahms Aktiengesellschaft, Hennigsdorf, Germany). The assay principle lies in Time-Resolved Amplified Cryptate Emission (TRACE) technology. The lower detection limit is 4.8 pmol/L and the functional assay sensitivity ($< 20\%$ interassay CV) is $< 12 \text{ pmol/L}$. The limit of quantification is 14.1 pmol/L (data from manufacturer). In our laboratory, the CV was found to be $< 5\%$ (4.4% at 28.86 pmol/L and 4.6% at 95.84 pmol/L).

Adjudication of the final diagnosis

Two independent cardiologists adjudicated the final diagnosis based on all medical charts; disagreements were settled

by consensus. ACS was defined as AMI or unstable angina. AMI was diagnosed when there was evidence of myocardial necrosis in association with clinical signs of myocardial ischaemia. Necrosis was diagnosed on the basis of a rising or falling pattern of cTnI concentration (conventional assay), with at least one value above the 99th percentile, at a level of imprecision of $< 10\%$ [7,20]. Unstable angina was diagnosed in the presence of: clinical manifestations suggestive of myocardial ischaemia, without evidence for myocardial necrosis; an ECG indicative of ongoing ischaemia or a $> 70\%$ stenosis of an epicardial coronary artery on coronary angiography ($> 50\%$ of the left main trunk); and the absence of an alternative diagnosis.

A non-ACS was defined in the presence of a cardiac but non-coronary diagnosis, non-cardiac origin or when the diagnosis remained unknown despite careful investigations.

Statistical analysis

The data are expressed as means \pm standard deviations for continuous variables, and numbers and percentages for categorical variables. As cTn and copeptin measurements may not have a normal distribution, they are reported as medians [25th–75th percentile]. Continuous variables were compared using Student's *t* test for normally distributed variables and the non-parametric Mann-Whitney test for non-normally distributed variables. Categorical variables were compared using the Chi² test or Fisher's exact test, as appropriate. ROC curves were generated to assess sensitivity and specificity throughout the concentration ranges of hs-cTnT and copeptin, and to compare the ability of hs-cTnT alone and in combination with copeptin to diagnose ACS, compared as suggested by DeLong et al. [21]. A *p* value < 0.05 was considered significant. The STATA statistical software, version 10.1 (StataCorp LP, College Station, TX, USA) was used for all analyses.

Results

Baseline characteristics and diagnosis of acute coronary syndrome

Fifty-eight patients fulfilled our inclusion criteria during the study period; their characteristics are reported in Table 1. The final adjudicated diagnosis was ACS in 30 patients, including 13 patients with AMI (non-ST-segment elevation myocardial infarction) and 17 patients with unstable angina; ACS was excluded in 28 patients. The diagnosis was based on complete medical charts that were available for all patients, including ECG record during chest pain in 33% of patients, echocardiography recorded on admission in 69% of patients, and coronary angiogram available data in 83% of patients. Patients with ACS as their final adjudicated diagnosis were older than those without ACS and had more frequent ST-segment changes on ECG; other characteristics were similar in both groups (Table 1).

Copeptin and high-sensitivity cardiac troponin T measurements

Hs-cTnT measured on admission was increased in patients with ACS as their final adjudicated diagnosis compared

Table 1 Baseline characteristics and presentation in the overall population and according to final diagnosis.

	All patients (n = 58)	Patients with ACS (n = 30)	Patients without ACS (n = 28)	P value ^a
Age (years)	57.9 ± 13.5	61.8 ± 13.6	53.7 ± 12.3	0.022
Men/women (n/n)	37/21	22/8	15/13	0.118
<i>Coronary risk factors</i>				
Hypertension	24 (41.4)	14 (46.7)	10 (35.7)	0.397
Hypercholesterolaemia	22 (37.9)	14 (46.7)	8 (26.7)	0.156
Diabetes	13 (22.4)	8 (26.7)	5 (17.9)	0.421
Obesity	19 (32.8)	11 (36.7)	8 (28.6)	0.512
Family history	20 (34.5)	7 (23.3)	13 (46.4)	0.064
Current smoking	19 (32.8)	8 (26.7)	6 (21.4)	0.591
<i>Past medical history</i>				
Myocardial infarction	12 (20.7)	5 (16.7)	7 (25.0)	0.434
Coronary revascularization	11 (19.0)	6 (20.0)	5 (17.9)	0.574
<i>Drug regimen</i>				
Aspirin	20 (34.5)	9 (30.0)	11 (39.4)	0.47
Clopidogrel	9 (15.5)	4 (13.3)	5 (17.9)	0.726
Beta-adrenergic blocker	18 (31.0)	8 (26.7)	10 (35.7)	0.457
ACE inhibitor or ARB	20 (34.5)	11 (36.7)	9 (32.1)	0.717
Statin	24 (41.4)	12 (40.0)	12 (42.9)	0.825
Duration of chest pain (hours)	3.2 ± 1.4	7.5 ± 8.6	7.6 ± 11.7	0.953
<i>Electrocardiogram</i>				
Q wave	7 (12.1)	6 (14.0)	4 (9.1)	0.477
ST-segment depression	12 (20.7)	10 (23.3)	3 (6.8)	0.039
T-wave inversion	16 (28.1)	20 (47.6)	12 (27.3)	0.051
<i>Echocardiography</i>				
Recorded on admission	40 (69.0)	32 (74.4)	30 (68.2)	0.520
Abnormal wall motion	11 (19.0)	13 (30.2)	6 (13.6)	0.061
<i>Screening blood tests</i>				
Creatinine (μmol/L)	94 ± 37	97 ± 28	91 ± 44	0.484
GFR (mL/min/1.73 m ²)	77 ± 20	73 ± 20	81 ± 20	0.111
cTnI > 0.07 μg/L on admission ^b	14 (46.7)	14 (46.7)	0 (0.0)	<0.001
cTnI > 0.07 μg/L at 6 hours ^b	18 (60.0)	18 (60.0)	0 (0.0)	<0.001

ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; GFR: glomerular filtration rate; cTnI: cardiac troponin I. Values are means ± standard deviations or numbers (%) of observations in the corresponding group, unless otherwise indicated.

^a Between patients with ACS and patients without ACS.

^b 0.07 μg/L is the 99th percentile of the method (cTnI), with a coefficient of variation > 10%.

with in patients without ACS (43 [14–108] vs 4 [2–8] ng/L, respectively; $p < 0.001$). Hs-cTnT measured on admission accurately detected 22 patients with ACS; hs-cTnT measurement at 3 and 6 hours resulted in the detection of three and four additional patients with ACS, respectively. Copeptin concentration measured on admission was not statistically different in patients with and without ACS (10.7 [7.2–22.2] vs 12.2 [6.0–27.8] pmol/L, respectively; $p = 0.687$). Indeed, copeptin concentration was 10.3 [6.5–14.9] pmol/L in patients with non-cardiac (or unknown) origin of chest pain and 38.4 [7.7–56.7] pmol/L in patients with cardiac but non-coronary cause of chest pain (cardiac syncope in one and acute heart failure in two patients). In addition, copeptin concentration was below the 14 pmol/L cutoff value in six patients with AMI as their final adjudicated

diagnosis; their main characteristics are summarized in Table 2.

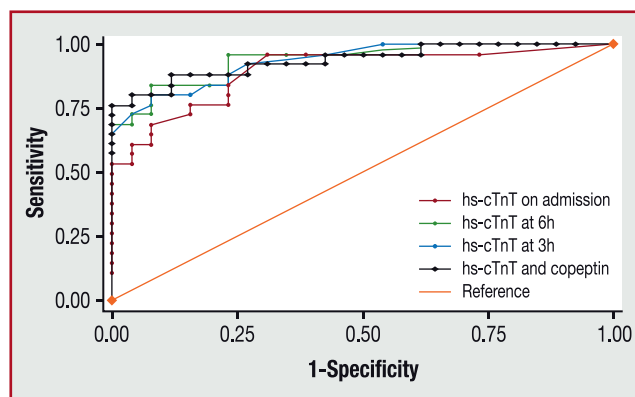
The combination of copeptin and hs-cTnT measured on admission accurately identified 26 patients with ACS as their final adjudicated diagnosis, including 13/13 patients with AMI. Table 3 shows the sensitivity, specificity and predictive values of hs-cTnT, copeptin and their combination in the detection of ACS.

The accuracy of ACS diagnosis, ascertained by area under the ROC curve, was 0.90 [95% confidence interval 0.81–0.99] for hs-cTnT measured on admission, 0.94 [0.88–1.00] for hs-cTnT measured at 3 hours, 0.94 [0.88–1.00] for hs-cTnT measured at 6 hours, and 0.94 [0.88–1.00] for the combination of hs-cTnT and copeptin measured on admission ($p = \text{not significant vs}$

Table 2 Characteristics of patients with acute myocardial infarction and no increase in copeptin concentration on admission.

ID	Age (years)	Sex	Risk factors	Previous AMI	Delay from onset of chest pain (hours)	GFR (mL/min/1.73 m ²)	ST-segment depression	Hs-cTnT on admission (ng/L)	Copeptin on admission (pmol/L)
1	37	Male	Obesity	No	3.3	86.7	Yes	150	7.3
2	67	Male	Current smoker Hypercholesterolaemia	No	5.5	80.9	No	104	9.1
3	73	Male	Hypertension	No	4.8	71.8	No	54	4.0
4	53	Male	Hypertension	No	2.0	99.2	No	43	8.3
5	43	Male	Obesity Hypercholesterolaemia Hypertension	No	5.0	75.4	No	125	8.2
6	69	Female	Obesity Hypercholesterolemia Diabetes Hypertension Hypercholesterolaemia	No	3.0	56.0	Yes	113	4.0

AMI: acute myocardial infarction; GFR: glomerular filtration rate; Hs-cTnT: high-sensitivity cardiac troponin T; ID: patient identification number.

**Figure 1.** Receiver operating characteristic curves, illustrating the performance of the combination of copeptin with high-sensitivity cardiac troponin T (hs-cTnT) measured at admission, and hs-cTnT alone measured at admission, 3 hours and 6 hours, in the diagnosis of acute coronary syndrome.

hs-cTnT measured on admission, for each comparison) (Fig. 1).

Discussion

This prospective study examined the value of a dual marker strategy that combines a high-sensitivity assay of cTn (a sensitive marker of cardiac necrosis) and copeptin (a marker of endogenous stress) in patients with suspected ACS. Results were compared with a single strategy using hs-cTnT measured at admission, 3 hours and 6 hours. We observed that the combination of these markers ruled out ACS at presentation with a negative predictive value of 82.6%. In comparison, the negative predictive values of hs-cTnT measured on admission and after 3 hours were 76.5 and 83.9%, respectively.

The accurate identification of ACS is challenging [3,4]. Numerous studies have demonstrated the superiority of cTn over various other markers in the detection of AMI and overall ACS [5,6,22]. Despite the recent development of sensitive assays of cTn, enabling measurement of concentrations that are 10-fold lower than those previously measurable, duplicate measurements are advocated in order to increase the accuracy of the method [8,14]. Indeed, the retrospective analysis of the PROTECT-TIMI-30 trial suggested increased detection of unstable angina when cTn measurement is repeated after 2 and 8 hours [14], whereas Giannitsis et al. recommended hs-cTn measurement on admission and after 3 hours [8]. Our study is consistent with these studies, as the measurement of hs-cTnT 3 hours after admission resulted in the detection of 13% more patients. Such a diagnostic uncertainty after the first cTn measurement may have clinical and economic implications, and previous studies have estimated the additional cost to exceed one billion dollars annually in the USA [23,24].

As no marker has supplanted cTn, despite extensive research [22,25–27], many researchers have advocated multimarker testing [15]. The combination of cTn (a marker of cardiac necrosis) with markers of different origins and modes of release should theoretically add diagnostic information. Copeptin is the c-terminal part of the vasopressin

Table 3 Sensitivity, specificity and predictive value of high-sensitivity cardiac troponin T, copeptin and their combination in the final diagnosis of acute coronary syndrome.

	Sensitivity	Specificity	Predictive values	
			Positive	Negative
Hs-cTnT > 14 ng/L on admission ^a	73.3	92.9	91.7	76.5
Hs-cTnT > 14 ng/L at 3 hours ^a	83.3	92.9	92.6	83.9
Hs-cTnT > 14 ng/L at 6 hours ^a	86.7	92.9	92.9	86.7
Copeptin > 14 pmol/L on admission ^b	44.8	70.4	61.9	54.3
Copeptin > 14 pmol/L ^a or hs-cTnT > 14 ng/L ^b on admission	86.7	70.4	76.5	82.6

Hs-cTnT: high-sensitivity cardiac troponin T. Values are % of observations in the corresponding group.
^a 14 ng/L is the 99th percentile of the assay, with a coefficient of variation < 10%.
^b 14 pmol/L cutoff value is based on data from manufacturer and previous studies [19].

prohormone, and is equimolar to vasopressin. The pathophysiology of copeptin secretion is therefore independent of cardiac cell necrosis and involves endocrine stress response. The accuracy of copeptin in the detection of AMI has been recently highlighted [17–19]. In these studies, the accuracy of copeptin alone was limited, but it added incremental value to the conventional cTn assay, and was even more valuable early after the onset of symptoms [17,19]. In our study, we observed that six patients with AMI as their final adjudicated diagnosis had low concentrations of copeptin < 14 pmol/L. The measuring method we used may account in part for the observed low sensitivity. Indeed, our method for measuring copeptin is not as analytically sensitive as that used in other studies [17,19]. With the Lumitest® method used by Reichlin et al. (which has been shown to have a lower detection limit [0.4 pmol/L] and a better precision for low concentrations [19]), the time of analysis is more important (about 120 minutes vs 20 minutes for our method). Manufacturers should develop a more sensitive method of copeptin measurement, adapted to emergency practice, in order to secure copeptin's place in the list of AMI biomarkers [28]. In addition, most patients already had important elevation of cTn, questioning the validity of the reported delay from onset of chest pain to presentation, a factor known to be crucial with regard to copeptin concentration [19]. Lastly, only a few of these patients had diabetes, obesity or renal failure, factors that are associated with increased copeptin concentration [17,19,29].

The possible role of copeptin in the detection of unstable angina might be limited, according to Reichlin et al., as they observed a similar concentration of copeptin in patients with unstable angina and with non-cardiac cause of chest pain [19]. However, Keller et al. observed a slight improvement in the detection of ACS with copeptin in addition to cTn [17]. On the one hand, our results are concordant with the two studies cited above, as we observed no significant difference in c-statistics with the addition of copeptin to hs-cTnT. On the other hand, we also observed a slight improvement in the detection of ACS with the addition of copeptin, which is similar to the incremental value offered by repetition of the cTn measurement. This may have clinical implications, if confirmed in larger series, as it would result in earlier discharge of patients without ACS.

In this study, we examined the ability of our combination of markers to detect overall ACS. Given the large representation of unstable angina in our study and other studies, we assume that considering ACS, rather than AMI solely, is clinically relevant [30,31].

In this study, the ECG was recorded during chest pain in 33% of patients. In addition, echocardiography was recorded on admission in more than two-thirds of patients and angiograms were performed in > 80% of patients; we therefore assume that our adjudicated diagnoses were robust.

Limitations of our study

Our study is limited by the enrolment of a limited number of patients and by the inclusion of only one recruiting medical centre. The results, therefore, are preliminary and need to be confirmed and extended. In addition, our small sample size precluded any subgroup analysis. Although we enrolled patients admitted to the intensive care unit, we hypothesize that our results can be extrapolated to emergency departments, as long as the use of the assays is limited to patients presenting with suspected ACS based on a detailed clinical evaluation that includes ECG—a hypothesis to be confirmed in dedicated studies. As our study was observational, it did not measure the possible clinical effects of more accurate detection of ACS.

Conclusions

In conclusion, this prospective study demonstrated that a dual marker strategy that combined hs-cTnT with copeptin (both measured at admission), increased slightly the detection of ACS compared with the use of hs-cTnT alone, to a level similar to that achieved by repetition of hs-cTnT measurement; the ability of this strategy to enable earlier rule out of ACS needs to be assessed by further studies.

Conflict of interest statement

Dr Chenevier-Gobeaux has received honoraria from Brahms. Dr Meune has received lecture fees from Roche Diagnostics and Brahms.

Acknowledgements

The authors are indebted to Roche Diagnostics (Roche Diagnostics, Meylan, France), who provided the investigational kits for the assays of cTn, and to Brahms (Brahms, France), who provided the investigational kits for the assays of copeptin.

The funding sources had no role in the design of the study, the collection, analysis and interpretation of the data, the writing of the report or the decision to submit the paper for publication.

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